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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,066	10/19/2001	Michael Hallek	50125/019001	8894

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,066	HALLEK ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-27 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-27 are pending in this application. An IDS filed 03/19/01, Paper No. 3 has been received and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). The address of Michael Hallek and the address and citizenship of Anne Girod have been altered.

Claim Objections

Claims 1-27 are objected to because of the following informalities: Claims should begin with an article (e.g. "The" or "A"). Appropriate correction is required.

Claim Rejections - 35 USC § 101

Claim 27 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-10 and 17-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Mamounas et al WO 97/38723 publication date October 23, 1997 (provided by applicant), see entire document.

Mamounas et al teach AAV2 and AAV4 vectors with targeting molecules that bind to selected cell types incorporated into the structural proteins VP-1, VP-2 or VP-3 (see e.g. page 4, line 21-31). In conjunction with altered targeting by insertion of a targeting peptide or protein, binding at the wild-type receptor is deleted, for AAV this requires the 150 kD heparan sulphate proteoglycan (see e.g. page 3, line 9-15). Targeting molecules include targeting peptides or proteins such as C4 peptide or monoclonal antibody single chain fragments (see e.g. page 17, line 30 through page 19, line 10). For example, VP-1, VP-2 and VP-3 were incorporated at their N-terminus with C4 (see e.g. page 43, line 28-30) or were mutated to incorporate a single-chain fragment variable region of a monoclonal antibody against the CD34 molecule (sFv) at their N-terminus (see e.g. page 67, line 24-26). Following this mutation, rAAV were produced (see e.g. page 69, line 11-14). The resultant rAAV with sFV fused to VP-2 then was determined to have altered target specificity through interactions with CD34 molecules on KG-3 cells and the rAAV was also shown to have increased infectivity to these cells (page 69, line 15-26 and table 3).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-27 are vague for reciting the structural protein "characterized by ". It is unclear if the meaning of the term "characterized by" is open (i.e. comprising) or closed (i.e. consisting of). Use of the term "characterized by" is indefinite as it fails to establish the metes and bounds of the gene sequences encompassed by the claimed language.

Claim 1 recites the limitation "the virus" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 2 is unclear for reciting that the structural protein mutation is located on the virus surface. The relationship of the virus surface to the structural protein and/or the mutation is unclear from the claim. Is the mutated structural protein coincidently located on the surface of the virus or must the mutation reside in a domain of the structural protein that is located in the exterior of the virus surface?

Claim 2 recites the limitation "the virus surface" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 is vague for reciting that the mutation is in the N-terminus of the structural protein. The N-terminus is not defined as a domain or a specific set of base pairs but is a

vaguely defined region for which there is no clear beginning or end. Therefore, the metes and the bounds of the claimed region are unknown.

Claim 7 is vague for reciting that the structural protein is derived from AAV subfamilies. It is unclear how closely related the derived proteins are to the original AAV. It is also unclear what procedures were used to generate the derivative domains. The metes and bounds of the claimed subject matter are unclear.

Claim 8 is unclear for reciting that the mutation is "one or more deletions (insertions)" without noting what is deleted (inserted).

Claim 8 is unclear for reciting that the mutations can be a combination of this mutation. It would be remedial to recite "these mutations".

Claim 10 recites the limitation "the nature of the characteristic amino acid composition" in claim 9. There is insufficient antecedent basis for this limitation in the claim.

Claim 11-14 and 15-16 recites the limitation "the VP1-encoding nucleic acid" in claim 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitation "the XhoI cleavage site" in claim 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 recites the limitation "BsrBI cleavage site" in claim 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 13 recites the limitation "BsrBI/HindII cleavage sites" in claim 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 14 recites the limitation "in VP3" in claim 8. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 is unclear in reciting that the structural protein is in the form of an AAV particle particularly a capsid. It is unclear how a structural protein can be in the form of a viral particle as a particle is comprised of a variety of proteins and viral DNA.

Claims 18-27 are vague for reciting the structural protein "according to ". It is unclear if the meaning of the term "according to" is open (i.e. comprising) or closed (i.e. consisting of). Use of the term "according to" is indefinite as it fails to establish the metes and bounds of the gene sequences encompassed by the claimed language.

The phrase ""where appropriate, the expressed structural protein is isolated" in claim 20 renders the claim indefinite because it is unclear when the isolation of the structural protein is part of the claimed invention. See MPEP § 2173.05(d). It is unclear if the process has all of the components necessary to "produce" a structural protein in the absence of its isolation.

Claims 21-26 are unclear for reciting "medicinal products" and diagnostic aids". It is unclear what distinguishes the structural protein according to claim 1, the nucleic acid according to claim 18 and the cell according to claim 19 from a "medicinal product" or a "diagnostic aid". The metes and bounds of the claimed subject matter are unclear.

Claim 27 provides for the use of the structural protein in a method, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites a structural protein of AAV, which comprises at least one mutation. The mutated structural protein is capable of particle formation resulting in a viral particle with increased infectivity. This invention requires a complex combination of molecular cloning in combination with viral and cell culture techniques to generate mutations in AAV structural proteins with assays for infectious particles and enhanced infectivity.

2) Scope of the invention. Claims 21-26 recite medicinal products and diagnostic aids comprising the structural proteins, nucleic acids and cells comprising the structural protein. The invention recites administration of the structural protein from AAV, nucleic acid encoding the structural protein and cells comprising the nucleic acids encoding the structural protein of the

claimed invention as a medicinal product and diagnostic aid. Recited uses include somatic gene therapy. No other recited use for the medicinal products other than in gene therapy is disclosed. No recited use for diagnostic aids other than for therapeutic diagnosis is provided.

3) Number of working examples and guidance. The instant specification fails to demonstrate any examples or specific guidance for compositions of AAV with mutation(s) in a structural protein suitable as a medicinal product or diagnostic aids. Applicants teach on page 15, line 11-19 that medicinal products and diagnostic aids comprise a nucleic acid or cell of the invention "and where appropriate, additives, such as, for example, a physiological saline solution, stabilizers, proteinase inhibitors etc". This guidance is general and broad. Applicant teaches mutations of VP-1 and VP-3 and insertion of a laminin P1 ligand for altered binding to M07-LP1-R and B16F10 cells.

4) State of the art. There has been much interest in the development of viruses that transduce therapeutic genes into target tissues. However, the lack of established protocols and positive results has hampered the use of such inventions. The art must therefore be considered to be poorly developed.

5) Unpredictability of the art. Adeno-associated viral vectors are non-pathogenic viruses that are widespread in the human population about 80% of humans have antibodies against AAV (Anderson, Nature, Vol 392 page 28, column 1). The approach of the present application is to generate a mutation in a structural protein such that specificity and infectivity is altered and to use it as a medicinal product to deliver genes to cells. However, rAAV use in gene therapy is still specifically hindered as it carries the risk of disrupting functioning genes by randomly insert itself into the chromosome. While wild type AAV integrates exclusively into chromosome 19,

rAAV integrate much less efficiently and more randomly (Anderson, page 28, column 2). Another large obstacle to overcome in the use of rAAV in gene therapy is the laborious nature of the generation of these vectors in high quantities (Kmiec, American Scientist Vol 87, 1999, page 243, column 3) and rAAV cannot integrate into non-dividing cells (Anderson, page 28, column 2). For gene therapy to be successful, an appropriate amount of therapeutic gene must be delivered into the target tissue. Finally, given the high number of the population that carries antibodies to AAV, immunogenicity towards rAAV may confound efforts to use AAV as a gene carrier (Verma and Somia, page 241, column 3).

The unpredictability of use of the instantly claimed invention in humans is accentuated by the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use such as tumor cell selectivity in humans, lack of toxicity to normal tissues, and the effect of the antiviral immune response as well as doses to be administered, dose schedules etc. For example, what level of expression is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication? The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Meng and Deiry (Gene Therapy of Cancer, 1999, page 6, column 1) teach that means of delivery other than intratumoral injection compound the obstacles associated with adenoviral use. "Tropism for organs such as liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous of the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass". "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a

needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, p 1165, column 2).

6) Amount of Experimentation Required. The invention recites use of a structural protein mutated such that it is capable of particle formation with enhanced infectivity, nucleic acids that encode the structural protein and cells as medicinal products or diagnostic aids (i.e. therapeutic applications). In view of the unpredictability of the art of therapeutic gene expression in mammalian subjects, the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of structural proteins with at least one mutation that is capable of particles formation that results in the increased infectivity of virus containing the mutated structural protein.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus. The instantly claimed invention recites that a structural protein is mutated such that it is capable of forming infectious particle and the infectivity of the particle is increased. Applicant teaches us that there are many means of mutating the structural protein including point mutations, mutations of several amino acids, deletion or insertion mutations and combinations of these mutations. The outcome of the mutations is ultimately altered cell-targeting specificity mediated by the mutated structural protein such that the resultant AAV–cell interactions are increased leading to an increase in infectivity. The specification teaches insertion of a laminin P1 ligand into two AAV structural proteins, VP1 and VP3 (pages 16-20). The resultant virus is shown to have increased infectivity of M07-LP1-R and B16F10 cells. It is also mentioned that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication is given about the ability of the structural protein to form particles or the infectivity of a virus containing the mutated structural protein. The disclosure of P1 ligand to alter specificity to the two cell types is not accompanied by a disclosure as to its relative property required for the ability to alter infectivity in any cell

type. Therefore, there is no clear description of the structural or functional characteristics required for a mutations in other structural proteins encompassed by the claims with other ligands to increase infectivity. Neither applicant nor the prior art provide a correlation between the structure of the P1 and its ability to alter infectivity. Given the large number of mutations envisioned by the invention and the diversity of the cellular receptors and ligands encompassed by the claims and the inability to determine which mutation will increase infectivity, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER

MM